REMARKS

Claims 1-2 and 4-15 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Makovec et al. (US 5,130,474), in view of Midler et al. (US 5,314,506), and further in view of Green (US 7,122,083).

Applicants respectfully traverse the rejection.

Claim 1 is directed to a method for the preparation of crystalline dexloxiglumide by crystallization of the crude product from solvent, characterized in that isopropyl ether is used as solvent, wherein the crystallization step is performed by adding a seeding of microcrystalline dexloxiglumide having an average particle size (D50) ≤ 20 μm to a supersaturated solution of crude dexloxiglumide; wherein the dexloxiglumide is in crystalline particle form having a percentage by volume of less than 15% of fine particles having dimensions less than 10 μm, and an average particle size value (D50) of between 50 and 130 μm.

In the present invention, isopropyl ether is used as a solvent and crystalline dexloxiglumide having a percentage by volume of less than 15% of fine particles having dimensions less than 10 μm and an average particle size value (D50) of between 50 and 130 μm, which are advantageous rheological properties that are suitable for the use of it in preparation of tablets.

Makovec discloses a crystallization method using a water/alcohol mixture. As the Examiner acknowledges, Makovec does not disclose a crystallization method using isopropyl ether for dexloxiglumide. In addition, Makovec does not disclose a crystallization method by adding a seeding of microcrystalline dexloxiglumide. To make up the deficiencies, the Examiner relies upon Midler and Green.

It is respectfully submitted that there is no motivation to combine the references, and even if the references were somehow combined, the claimed invention would not be achieved.

First, Midler describes a completely different method that provides for the use of a solvent and an anti-solvent to give regular crystals, but with a much finer particle size distribution (25 μm or lower). Since the final particle size of Midler is smaller than the claimed particle size, the object of Midler is contrary to that of the present invention. Thus, one of ordinary skill in the art would not be motivated to combine the references to arrive at the claimed invention based on the disclosure of Midler.

In addition, although Midler discloses that seeding may be helpful, Midler is silent regarding seeding with microcrystalline dexloxiglumide having an average particle size (D50) ≤ 20 μm. Thus, even if the references were somehow combined, the combination would not result in the claimed seeding step since Milder does not disclose seeding with microcrystalline dexloxiglumide having the claimed average particle size.

Second, Green describes examples that use of aqueous solutions of adipic acid (Examples 1,2,3 and 4) or glycine (Example 5) or cisteine (Example 6). Therefore, Green uses different substances (water soluble) with different solvents.

It is also noted that the apparatus used by Green is much more complicated than the simple apparatus used for the preparation of dexloxiglumide, and requires - among others - the use of an ultrasonic bath, which can be easily applied on a laboratory scale, but which is difficult to apply on an industrial scale. Indeed, Green teaches controlled seeding using an ultrasound and thus, there is no teaching in Green regarding controlled seeding using particular particle size or the use of isopropyl ether. Thus, one of ordinary skill in the art would not be motivated to modify Makovec by adding a seeing step using microcrystalline dexloxiglumide having the claimed average particle size to arrive at the claimed invention.

Furthermore, even if the references were somehow combined, the combination would not result in the claimed invention since Green is silent regarding the use of microcrystalline dexloxiglumide having a particular particle size.

For at least the above reasons, it is respectfully submitted that a *prima facie* case of obviousness has not been established.

Moreover, the present invention provides unexpectedly superior results. Specifically, Makovec discloses a crystallization method using a water/alcohol mixture. This method provides a product having negative rheological properties, such as to hinder its use in making solid oral preparations in the form of tablets. As shown in Fig. 1B, when a water-alcohol (ethanol) mixture is used, the dexloxiglumide has a D50 of 23.64 and a span index of 4.668. Thus, the dexloxiglumide does not possess the advantageous features of the claimed dexloxiglumide.

In addition, a comparative example was prepared in which the seeding step was omitted and isopropyl ether was used. The product obtained possessed a D50 of 15.025 μm and a Span index of 3.85. Thus, the dexloxiglumide does not possess the advantageous features of the claimed dexloxiglumide.

The above comparative example also demonstrates the synergistic effect of the use of isopropyl ether and seeding step of the claimed invention, which was unexpected.

In sum, the advantageous results obtained by the crystallization method of the present invention were unexpected, particularly when compared with the prior art references.

In view of the above, it is respectfully submitted that the present claims are patentable over the cited art and withdrawal of the rejection is respectfully requested.

For the foregoing reasons, reconsideration and allowance of claims 1-2 and 4-15 is respectfully requested.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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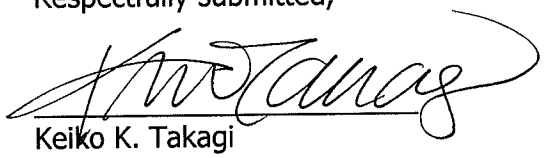
Respectfully submitted,



Keiko K. Takagi
Registration No. 47,121

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
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